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ORIGINAL ARTICLE

Association of diabetes mellitus and metformin use with biochemical recurrence in patients treated with radical prostatectomy for prostate cancer

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Abstract
Purpose The impact of diabetes mellitus (DM) and metformin use on biochemical recurrence (BCR) in patients treated with radical prostatectomy (RP) remains controversial.
Methods We retrospectively evaluated 6,863 patients who underwent RP for clinically localized PC between 2000 and 2011. Univariable and multivariable Cox regression models addressed the association of DM and metformin use with BCR.
Results Overall, 664 patients had a diagnosis of DM from which 287 (43 %) were on metformin and 377 (57 %) were on anti-diabetics other than metformin. DM and metformin were not associated with any clinicopathologic features (p values >0.05). Within a median follow-up of 25 months (interquartile range 35 months), 774 (11.3 %) patients experienced BCR. Actuarial 5-year biochemical-free survival was 83 % for non-diabetic, 79 % for diabetic patients without metformin use, and 85 % for diabetic patients with metformin use (log rank $p = 0.17$). In uni- and multivariable Cox regression analyses with the non-diabetic group as referent, DM without metformin use (HR = 0.99; 95 % CI 0.75–1.30, $p = 0.65$) and DM with metformin use (HR = 0.84, 95 % CI 0.58–1.22, $p = 0.36$) were not associated with BCR after RP. A subgroup analysis stratified by nodal status, surgical margins, tumor stage, and

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Gleason sum did not reveal any significant association between DM, use of metformin and risk of BCR.
Conclusions We found no association between DM or metformin use and cancer-specific features or BCR in patients treated with RP. The effect of DM and metformin on complications, wound healing and overall survival needs to be assessed in similar cohorts.

Keywords Prostate cancer · Radical prostatectomy · Diabetes mellitus · Metformin · Biochemical recurrence

Introduction

Radical prostatectomy (RP) is one of the most widely used treatment approaches in patients with clinically localized prostate cancer (PC) [1]. Unfortunately, up to 40 % of patients experience disease recurrence during long-term follow-up despite apparently successful surgery [2]. The impact of diabetes mellitus (DM) on the incidence and natural history of PC remains controversial [3–5]. The results of a recent meta-analysis suggest that diabetes mellitus is associated with decreased incidence of prostate cancer [4]. In contrast, in men with PCa, preexisting DM appears to be associated with a higher risk of recurrence, suggesting that DM may affect disease progression following RP [6].

Metformin is a biguanide derivate and one of the most commonly used oral drugs for non-insulin-dependent DM. Studies suggested a significant association of metformin with favorable cancer outcomes of diabetic patients in various malignancies [7–12]. Increased cumulative duration of metformin exposure after PC diagnosis was found to be associated with decreased cancer-specific and any-cause mortality in diabetic men [13]. Furthermore, metformin appears to reduce the development of castration-resistant PC and cancer-specific mortality in patients treated with external beam radiation therapy (EBRT) [14]. In contrast, metformin use was not associated with decreased risk of BCR in a study on patients with PC treated with RP [15]. These results are further confirmed by another recent study, which found metformin use not associated with risk reduction in BCR and any-cause mortality in patients treated with RP [16]. Based on the conflicting results of studies in PC, the association of DM and metformin with BCR warrants further analysis in a large cohort. We therefore hypothesized that DM is associated with the features of biologically aggressive PC, while metformin exerts a protective effect. For this purpose, we assessed a large multicenter cohort of patients treated with RP for clinically localized PC.

Subjects/patients and methods

Patient selection and data collection

This was an institutional-review-board-approved study, with all participating sites providing the necessary institutional data sharing agreements prior to the initiation of the study. A computerized databank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Prior to analysis, the database was closed and the final data set was produced. A total of eight US and European centers provided data. The study cohort included 7,447 patients with clinically localized PC treated with RP between 2000 and 2011. Patients with preoperative PSA > 50 ng/ml ($n = 15$), missing preoperative PSA ($n = 57$), surgical margin status ($n = 13$), lymph node status ($n = 54$), RP Gleason score ($n = 32$), and/or missing follow-up data ($n = 463$) were excluded from the analysis. This left 6,863 patients for analysis. No patient received preoperative radiotherapy, hormonal treatment, or chemotherapy. No patient had distant metastatic disease at the time of RP.

Pathological evaluation

All surgical specimens were processed according to standard pathologic procedures as outlined elsewhere [17]. Genito-urinary pathologists assigned pathologic stage, which was reassigned according to the 2007 American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging system when necessary. Lymphoid tissue removed was submitted for histological examination. Positive pathological margin was defined as tumor cells in contact with the inked surface of the prostatectomy specimen.

Follow-up

Follow-up (FU) was performed according to institutional protocols. Generally, patients were seen postoperatively quarterly within the first year, semiannually in the second year, and annually thereafter. Digital rectal examination and prostate-specific antigen (PSA) evaluation were performed at each visit. The primary endpoint BCR was defined as PSA value >0.2 ng/ml on two consecutive visits [1]. The date of BCR were attributed to the day of the first PSA. In case of lymph node metastasis, immediate adjuvant androgen deprivation therapy was initiated. No patient received immediate postoperative radiotherapy.

Statistical analysis

Associations of DM with and without metformin use with categorical variables were assessed using χ^2 test. Differences in continuous variables were analyzed using the Mann–Whitney *U* test. BCR-free survival curves were generated using the Kaplan–Meier method; log-rank test was applied for pairwise comparison of survival. Univariable and multivariable Cox regression models addressed the association of DM with and without metformin use with BCR after RP. All *p* values were two-sided, and statistical significance was defined as a $p < 0.05$. Statistical analyses were performed using SPSS Statistics® 20 (SPSS®, IBM Corp, Armonk, NY, USA).

Results

Association of diabetes mellitus and metformin use with clinicopathologic characteristics

Table 1 shows the clinicopathologic characteristics of the 6,863 patients and their association with DM and metformin use. A total of 664 (9.7 %) patients had DM, 287 (4.2 %) were taking metformin at the time of RP. There was no difference in age, preoperative PSA, biopsy or RP Gleason sum, pathologic tumor stage, lymph node status or surgical margin status between non-diabetics, diabetics using metformin, and diabetics not using metformin.

Association between diabetes mellitus and biochemical recurrence

Within a median follow-up of 25 months (interquartile range 35 months), 774 (11.3 %) patients experienced BCR; 689 (11.1 %) non-diabetic; and 85 (12.8 %) diabetic patients. Actuarial estimates of BCR-free survival were 90 % (standard error ±0), 83 % ± 1, and 76 % ± 1 for non-diabetics and 89 % ± 1, 82 % ± 2, and 74 % ± 3 for diabetics at 3, 5, and 7 years, respectively ($p = 0.38$) (Fig. 1). In univariable Cox regression analyses, DM ($p = 0.38$) was not associated with BCR, whereas age ($p = 0.001$), preoperative PSA ($p < 0.001$), RP Gleason sum ($p < 0.001$), lymph node metastasis ($p < 0.001$), positive surgical margins ($p < 0.001$), extracapsular extension ($p < 0.001$), and seminal vesicle invasion ($p < 0.001$) were all associated with BCR.

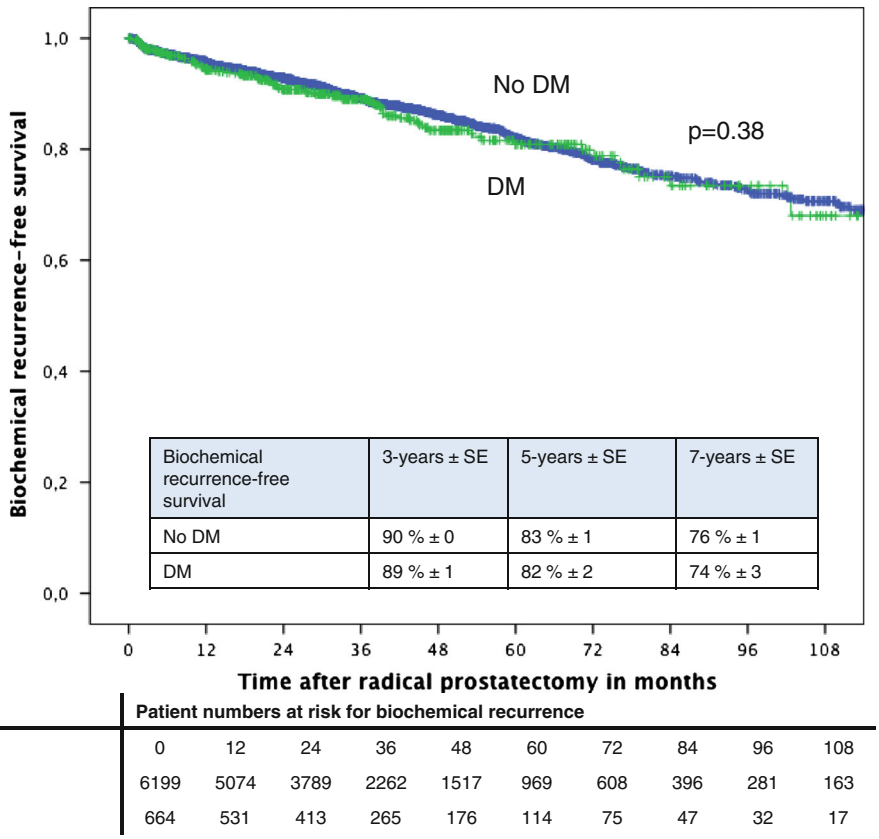
Association between metformin use and biochemical recurrence

Within follow-up, 56 (14.9 %) patients with DM and no metformin use and 29 (10.1 %) patients with DM and metformin use experienced BCR. Actuarial estimates of BCR-

Table 1 Clinicopathologic characteristics of 6,863 patients who underwent radical prostatectomy for clinically localized prostate cancer

Characteristics	Total	No DM	DM, no metformin use	DM, metformin use	*p* values
Number of patients (*n*, %)	6,863	6,199 (90.3)	377 (5.5)	287 (4.2)	–
Age (years)					
Mean (SD)	61.3 (6.7)	61.2 (6.7)	61.3 (6.4)	61.5 (6.3)	0.66
Median (IQR)	61.5 (57–66)	61.5 (57–66)	61.6 (58–66)	61.5 (57–66)	
Preoperative PSA (ng/ml)					
Mean (SD)	7.5 (4.9)	7.5 (4.8)	7.8 (5.9)	7.6 (5.7)	0.18
Median (IQR)	6.2 (4.5–9.0)	6.2 (3.9–8.5)	6.0 (3.9–8.1)	5.9 (3.8–7.6)	
Preoperative Gleason sum (*n*, %)					
≤6	3,778 (55.0)	3,423 (55.2)	203 (53.7)	152 (53.0)	0.78
7	2,657 (38.7)	2,387 (38.5)	154 (41.0)	116 (40.4)	
≥8	428 (6.3)	389 (6.3)	20 (5.3)	19 (6.6)	
RP Gleason sum (*n*, %)					
≤6	2,080 (30.3)	1,865 (30.1)	122 (32.4)	93 (32.4)	0.13
7	4,266 (62.2)	3,881 (62.6)	217 (57.6)	168 (58.5)	
≥8	517 (7.5)	453 (7.3)	38 (10.1)	26 (9.1)	
Extracapsular extension (*n*, %)	1,273 (18.5)	1,132 (18.3)	85 (22.5)	56 (19.5)	0.11
Seminal vesicle invasion (*n*, %)	467 (6.8)	412 (6.6)	32 (8.5)	23 (8.0)	0.27
Positive surgical margin (*n*, %)	1,021 (14.9)	925 (14.9)	58 (15.4)	38 (13.2)	0.71
Lymph node metastasis	772 (11.2)	692 (11.2)	46 (12.2)	34 (11.8)	0.78

DM diabetes mellitus, *RP* radical prostatectomy, *SD* standard deviation, *IQR* interquartile range



Biochemical recurrence-free survival	3-years ± SE	5-years ± SE	7-years ± SE
No DM	90 % ± 0	83 % ± 1	76 % ± 1
DM	89 % ± 1	82 % ± 2	74 % ± 3

Fig. 1 Kaplan–Meier curves depicting biochemical recurrence-free survival in 6,863 patients treated with radical prostatectomy for prostate cancer, according to diabetes mellitus (DM)

Patient numbers at risk for biochemical recurrence										
Months	0	12	24	36	48	60	72	84	96	108
No DM	6199	5074	3789	2262	1517	969	608	396	281	163
DM	664	531	413	265	176	114	75	47	32	17

free survival were 87 % ± 2, 79 % ± 3, and 71 % ± 5 for diabetics without metformin use and 92 % ± 2, 85 % ± 3, and 79 % ± 5 for diabetics with metformin use at 3, 5, and 7 years, respectively. No significant differences in BCR-free survival could be found between non-diabetics and diabetics with metformin use ($p = 0.51$), non-diabetics and diabetics without metformin use ($p = 0.08$), and diabetics with and without metformin use ($p = 0.10$). In univariable and multivariable Cox regression analyses, DM with or without metformin use was not associated with BCR, whereas preoperative PSA ($p < 0.001$), RP Gleason sum ($p < 0.001$), lymph node metastasis ($p < 0.001$), positive surgical margins ($p < 0.001$), extracapsular extension ($p < 0.001$), and seminal vesicle invasion ($p < 0.001$) were all associated with BCR (Table 2).

A subgroup analysis in patients with and without lymph node metastasis, negative and positive surgical margins, capsular invasion and seminal vesicle invasion as well as categorized Gleason sum (≤6, =7, ≥8) did not reveal any significant association between DM, metformin use, and BCR in uni- and multivariable analyses (Table 2).

Discussion

In our study, we could not detect a significant association between DM and increased risk of BCR in patients treated with RP. This stands in contrast to the results of a previous study on the association of DM with PCa outcomes after RP, which found DM independently to be associated with a 55 % increase in risk of BCR [15]. One explanation for these contradictory results might be that the rate of positive surgical margins and positive lymph nodes in this study was higher in diabetic patients. As positive surgical margins [18] and positive lymph nodes [19] are well-known risk factors for BCR, differences in clinicopathologic features might have driven the results of the aforementioned study toward a higher rate of BCR in DM patients. Similar to the results of our study, a previous study does not reveal a beneficial effect of metformin use on the outcome of patients with PCa after RP [15]. These findings are further supported by a recent study, which found no association between metformin use and PC outcomes in diabetics following RP [16]. In contrast, Spratt et al. [14] reported metformin use to be associated with a lower BCR rate and PC-specific mortality in patients treated with EBRT for clinically localized PC compared to diabetics not using metformin and non-diabetic patients. A possible explanation for the positive effect of metformin use on the outcome of PC treated with EBRT is a potential synergism between metformin and ionizing radiation. Both metformin and ionizing radiation have been shown to activate the AMP kinase pathway that leads to the downregulation of cell growth, cell cycle progression, and angiogenesis [20, 21].

Table 2 Univariable and multivariable Cox regression analyses predicting biochemical recurrence in patients treated with radical prostatectomy for prostate cancer in relation to DM and metformin use

Patient subgroup	Univariable			Multivariable		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
All patients[a]						
No DM	–	Referent	0.17	–	Referent	0.65
DM, no metformin	1.27	0.97–1.67	0.08	0.99	0.75–1.30	0.92
DM, metformin	0.88	0.61–1.28	0.51	0.84	0.58–1.22	0.36
No lymph node metastasis[b]						
No DM	–	Referent	0.11	–	Referent	0.36
DM, no metformin	1.3	0.98–1.71	0.07	0.98	0.73–1.30	0.87
DM, metformin	0.82	0.55–1.22	0.33	0.75	0.50–1.12	0.16
Lymph node metastasis[b]						
No DM	–	Referent	0.48	–	–	–
DM, no metformin	1	0.31–3.23	0.99			
DM, metformin	1.88	0.68–5.26	0.23			
Negative surgical margins[c]						
No DM	–	Referent	0.53	–	Referent	0.76
DM, no metformin	1.21	0.86–1.70	0.27	1.09	0.77–1.53	0.63
DM, metformin	0.99	0.65–1.52	0.97	0.89	0.58–1.37	0.6
Positive surgical margins[c]						
No DM	–	Referent	0.17	–	Referent	0.38
DM, no metformin	1.45	0.92–2.29	0.11	0.98	0.61–1.57	0.93
DM, metformin	0.7	0.33–1.49	0.36	0.59	0.28–1.25	0.16
Stage pT3a/b[d]						
No DM	–	Referent	0.96	–	Referent	0.51
DM, no metformin	0.97	0.67–1.41	0.89	0.82	0.56–1.19	0.3
DM, metformin	0.94	0.59–1.51	0.8	0.87	0.54–1.40	0.57
RP Gleason sum ≤ 6[e]						
No DM	–	Referent	0.51	–	Referent	0.44
DM, no metformin	1.08	0.55–2.14	0.82	1.11	0.56–2.19	0.77
DM, metformin	0.52	0.16–1.63	0.26	0.48	0.15–1.53	0.22
RP Gleason sum $= 7$[e]						
No DM	–	Referent	0.65	–	Referent	0.93
DM, no metformin	1.19	0.82–1.72	0.37	1.07	0.74–1.56	0.7
DM, metformin	0.96	0.60–1.53	0.85	1.01	0.63–1.61	0.98
RP Gleason sum ≥ 8[e]						
No DM	–	Referent	0.36	–	Referent	0.54
DM, no metformin	1.39	0.84–2.31	0.2	1.04	0.61–1.78	0.89
DM, metformin	0.82	0.40–1.68	0.59	0.67	0.32–1.38	0.27

CI confidence interval, *HR* hazard ratio, *RP* radical prostatectomy

[a] Multivariable Cox regression corrected for age, PSA value, RP Gleason score, lymph node metastasis, positive surgical margins, extracapsular extension, seminal vesicle invasion

[b] Multivariable Cox regression corrected for age, PSA value, RP Gleason score, positive surgical margins, extracapsular extension, seminal vesicle invasion. Because of low number of events, multivariable analysis could not be performed for node positive group

[c] Multivariable Cox regression corrected for age, PSA value, RP Gleason score, lymph node metastasis, extracapsular extension, seminal vesicle invasion

[d] Multivariable Cox regression corrected for age, PSA value, RP Gleason score, lymph node metastasis, positive surgical margins

[e] Multivariable Cox regression corrected for age, PSA value, lymph node metastasis, positive surgical margins, extracapsular extension, seminal vesicle invasion

Increased cumulative duration of metformin exposure after PC diagnosis was also found to be associated with decreased cancer-specific and any-cause mortality in diabetic men [13]. Furthermore, an analysis of the impact of metformin use on survival in 233 PC patients revealed metformin use as significant predictor of overall survival in multivariate analysis [22]. While our analyzed patient cohort consisted of clinically localized PC, the population of the two aforementioned studies encompassed patients with advanced PC, and only a low number of patients were treated with RP. One explanation for theses seemingly contradictory findings regarding the impact of metformin on PCa outcomes could be that metformin's antiproliferative effect can only be exerted when the cancer is present. A recent study showed that metformin decreased glucose oxidation and increased dependency on reductive glutamine metabolism both in cancer cell lines and in a mouse model of prostate cancer [23]. Furthermore, metformin has been shown to inhibit the inflammatory response associated with cellular transformation and cancer stem cell growth in vivo and in vitro [24]. As RP significantly alters the natural history of the cancer, it possibly abrogates the potentially antiproliferative effect of metformin. Another explanation for the survival benefit of PCa patients taking metformin might be associated with the cardiovascular effects of antidiabetic drugs. A recent study on mortality and cardiovascular risk of different insulin secretagogues and metformin showed that most of the insulin secretagogues appear to be associated with increased cardiovascular risk and mortality [25]. Thus, the survival benefit in patients taking metformin might be related to its positive cardiovascular properties rather than its potential antiproliferative effect.

While prediction of BCR is most crucial in the management of patients with PC, its association with clinicopathologic features is also important. We did not find any association between DM or metformin use and clinicopathologic features in patients treated with RP for clinically localized PC. This in accordance with a recent study, which found no significant differences in preoperative PSA, post-RP Gleason score, pathologic stage, positive surgical margins, or positive lymph nodes between diabetic patients using and not using metformin [16]. In addition, Patel et al. [15] reported no differences in preoperative PSA, post-RP Gleason score, and pathologic stage among men who underwent RP. In contrast to our study results, they found an association of DM with increased risk of positive surgical margins and positive lymph nodes compared to non-diabetic patients. Another recent study in patients treated with EBRT reported that patients with DM had a significantly higher proportion of Gleason $\geq$8 tumors than the control group (26.0 vs. 16.2 % $p < 0.05$) [14]. The patients in this study, however, were older than those in ours (69 vs. 62 years), so that a migration toward higher grade might explain the higher proportion of Gleason $\geq$8 tumors in that study.

Our study has several limitations. These include the retrospective design and the lack of information on dosage and duration of metformin intake prior to and after RP. This is specifically relevant in light of lacking impact of metformin use on pathologic features of PC at RP. The follow-up duration of our study is relatively short to draw a final conclusion on the impact of DM and metformin use on BCR in this cohort. Furthermore, information on the BMI of patients was missing, so that we could not adjust for this potential prognostic factor [26]. Moreover, we lacked information on preoperative serum levels of insulin and insulin-like growth factors. However, the correlation between preoperative IGF-I levels and risk of BCR after RP in patients with clinically localized PC has not been demonstrated [27]. Our study incorporates one of the largest cohorts of patients published so far on DM, metformin, and RP and confirms previously published data that metformin does not influence BCR after RP [15].

Conclusions

In our retrospective analysis, DM or metformin use was not associated with clinicopathologic features and BCR in patients treated with RP for PC. The potential effect of metformin on PC development needs further investigation. The effect of DM and metformin on complications, wound healing, and overall survival needs to be assessed in cohorts with long-term follow-up.

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Conflict of interest A Bachmann is on the advisory board of American Medical Systems and principal investigator of the GOLIATH study. S.F. Shariat is on the advisory board of Ferring Pharmaceuticals.

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